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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,744	03/13/2006	**Bandi Parthasaradhi Reddy**	H1089/20032	9862

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

NOTIFICATION DATE	DELIVERY MODE
11/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/571,744	PARTHASARADHI REDDY ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10-16,18,21-25,27 and 30-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 10-16, 18, 21-25, 27 and 30-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-17-10 has been entered.

Applicant's amendment of 2-17-10 has been fully considered. Applicant's argument has not been persuasive to overcome the previous rejections of 112/2nd paragraph, 102 and 103 based on **Manoury** (US'007). Thus, all previous rejections are still outstanding herein.

Claims 6, 8, 9, 17, 19, 20, 26, 28 and 29 are cancelled.

Claims 1-5, 7, 10-16, 18, 21-25, 27, and 30-61 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 7, 16, 18, 27, 34-46 and 51-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons are reiterated:

a. Claim 16 recites the term "***anti-solvent***" which has indefinite metes and bounds because there is no definition for said term in the specification. It is unclear if this is another reagent, or a device, or a process.

Applicant cites from the specification paragraphs [0011] and [0015] the description of an "anti-solvent" which is to cool, seed or partially remove solvent, and then concludes that "it is clear from the Specification that the anti-solvent is added to initiate or force crystallization of a solute from a solution." However, such a description does not clearly define what constitutes an "anti-solvent" in term of a chemical formula, a reagent or a mechanical mean. Thus, it is still not clear from the claims or the specification what is used as an "anti-solvent" to cool, seed or partially remove solvent.

b. Claim 34 and claims dependent thereon recite the limitation of "***activated tetrahydro-2-furoic acid***" which is not clear how it differs from the usual *tetrahydro-2-furoic acid*.

Applicant cites from the specification, paragraph [0020] which describes the "activated tetrahydro-2-furoic acid" as "tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form." Such an explanation does not clearly define the activated form is. What groups or moieties constitute "a conventional activated form" of the carboxylic acid in term of a terminal group.

c. Claim 7 is rejected as being dependent on the cancelled claim 6.

d. Claim 18 is rejected as being dependent on the cancelled claim 17.

e. Claim 27 is rejected as being dependent on the cancelled claim 26.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-5, 7, 10-16, 18, 21, 23, 34-36, 39, 41, 43, and 45-50 remain rejected under 35 U.S.C. 102(b) as being anticipated by **Manoury** (4,315,007 – cited on IDS). The alfuzosin base is described in Example I. The crystallization in alcoholic (e.g., isoamyl acohol) and/or ketonic solvent (e.g., acetone) can be found in Example I, column 3, lines 10-21, which states:

> A suspension of 3.7 g (0.02 mol) of the above amine and 4.8 g (0.02 mol) of 4-amino-2-chloro-6,7-dimethoxyquinazoline in 35 ml of isoamyl alcohol is then heated to the reflux temperature. The mixture is kept at the boil for 7 hours and left to stand overnight and the precipitate is then filtered off and washed with ethyl acetate and then with ether.
>
> The motor liquors from filtration are evaporated to dryness and the residue obtained is triturated with acetone. This yields a precipitate which is combined with the first and the whole is cyrstallised from a mixture of ethanol and ether. N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methyl-N_2-(tetrahydrofuroyl-2)-propylenediamine hydrochloride, which melts at 235° C. (decomposition), is thus obtained.

The above excerpt describes the process of making the free base of alfusozin by reacting N_1-Methyl-N_2-tetrahydrofuroylpropylenediamine (otherwise known as "**the above amine**") with

4-amino-2-chloro-6,7-dimethoxyquinazoline in isoamyl alcohol and then heated which produces a **"precipitate"** that is **the free base of alfuzosin** which at this point gets "crystallized from a mixture of ethanol and ether". The HCl salt at the end requires an additional step of acid addition salt which is not described because there is no mention of adding HCl acid prior to the step of crystallization the free base in ethanol and ether. Therefore, Example I clearly teaches the process of making a crystalline alfuzosin base.

While applicant argues that the step of **adding 2-N sodium hydroxide** in Example II does not produce an alfuzosin base, applicant's attention is directed to the preceding step in which tetrahydrofuroic acid reacts with the HCL salt of N_1-(4-amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylpropylenediamine (otherwise known as "**the foregoing diemine**" – column 3, line 64) **to produce the HCL salt of alfuzosin** which gets converted into the free base by the addition of 2-N sodium hydroxide.

The process recited in claims 34-36 can also be found in Example II in which the *N_1-(4-amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylpropylenediamine* reacts with *tetrahydrofuroic acid* to yield alfuzosin base which gets converted to HCl salt in alcoholic solvent (i.e., 2-propanol).

The process recited in claims 23, 39, 41, 43, and 45-50 -- converting the HCl salt of alfuzosin to alfusozin base-- can be found in Example II at the step of adding 2-N sodium hydroxide to the residue.

In particular, Example I teaches the crystalline form of alfuzosin base, and Example II teaches the acid addition salt of said base. Thus, it is clear that both Examples I and II yield the free base of alfuzosin. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 10, 11, 22, 24, 25, 27, 30-33, 37, 38, 40, 42, 44 and 51-61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Manoury**. Said claims recite a process of crystallizing alfuzosin by using specific solvents such as: *methyl-isobutyl ketone, methanol, ethanol* which are not disclosed in Example I or II of Manoury. However, *methyl-isobutyl ketone* and *acetone* are both **ketones** having dipole moments that are close enough to allow one skilled in the art to replace *methyl-isobutyl ketone* with *acetone* for cost effective (see a print out from Wikipedia, keyword "Acetone"). Likewise, *isoamyl alcohol* and *ethanol* are both **alcohols** and have similar polarity, and would be exchangeable (see Wikipedia, keyword "Alcohol").

Applicants argued that the instant claims are drawn to "a process for the preparation of crystalline alfuzosin base in ketonic solvent selected from the group consisting of methyl ethyl

ketone, methyl isobutyl ketone, . . ." Applicants further argued that: "there is not a reasonable expectation that different solvents would result in the formation of crystalline alfuzosin base because it is known in the art the use of different solvents will produce different crystalline forms of a product." In addition, applicants cited Banga et. al. which lists factors affecting crystallisation for polymorph such as: solvent polarity, degree of supersaturation, temperature along with the cooling profile, additives, seeds, pH and agitation rate. As pointed out in the above 102 rejection, Example I teaches the crystalline alfuzosin base as the **final product** crystallized from a mixture of ethanol and ether. Example II teaches the step of acid addition salt of the alfuzosin base (otherwise known as the "residual amine") by adding ethanolic hydrogen chloride to the alfuzosin base in 2-propanol. Thus, the **Manoury**'s teaching uses solvents that have similar polarity and pH, and so, it would have been reasonable to expect a crystalline form from Alfusozin base.

Thus, at the time of the invention, it would have been obvious to develop the claimed process because it would have been within the level of the skilled chemist in this art to substitute one ketone or alcohol for another in the same family of alcohols for optimum yield. See the following MPEP excerpt:

> **Optimization Within Prior Art Conditions or Through Routine Experimentation**
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

> by routine experimentation." **In re Aller**, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also **Peterson**, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); **In re Hoeschele**, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see **Merck & Co. Inc. v. Biocraft Laboratories Inc.**, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); **In re Kulling**, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and **In re Geisler**, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Applicant contents that "the prior art relied upon by the Examiner does not teach or

The claims only differ by reciting different alcoholic or ketonic solvents at various temperatures which can easily be maneuvered as cited in the MPEP excerpt above. The criteria of obviousness also depend on the level of one skilled in the art. In this case, such a modification is well within the level of the skilled chemist to obtain optimum yield.

Thus, it is maintained that the crystalline alfuzosin bse and its HCl salt as well as the process of making them are obvious to one skilled in the art for the reason stated previously and for the explanation above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

10-12-10